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Original article

Impact of insulin resistance on 1-year clinical outcomes in non-diabetic patients undergoing percutaneous coronary intervention with drug-eluting stents

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ABSTRACT

Background: Insulin resistance (IR) is known to be a risk factor for coronary artery disease (CAD). We aimed to evaluate the impact of IR on 1-year clinical outcomes in non-diabetic CAD patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stents (DESs).
Methods and results: A total of 229 consecutive non-diabetic CAD patients treated with DESs were enrolled. Study population was divided into IR group [homeostasis model assessment (HOMA) index ≥ 2.5, $n = 54$] and non-IR group (HOMA index < 2.5, $n = 175$). Baseline clinical and procedural characteristics were similar between the groups except higher incidence of high-sensitivity C-reactive protein and lower incidence of multivessel disease as the target vessel in the non-IR group. There was a trend toward longer restenosis lesion length in the IR group at 6 months angiographic follow up but composite major clinical outcomes up to 1 year were similar between the two groups.
Conclusions: Despite worse trend in angiographic outcomes in the IR group (HOMA index ≥ 2.5), it was not translated into worse 1-year major clinical outcomes following PCI with DESs as compared to the non-IR group.

Introduction

Insulin resistance (IR) is defined as decreased sensitivity and responsiveness to metabolic action of insulin to target organs. In 1936 Himsworth suggested the first concept of IR [1]. He found some diabetic patients who required more doses of insulin for blood sugar control. He differentiated types of diabetes into insulin sensitive and insulin insensitive. IR with hyperinsulinemia is known to be associated with hypertension, glucose intolerance, obesity, and dyslipoproteinemias of low high-density lipoprotein cholesterol (HDL-C) levels or hypertriglyceridemias, which are well-known risk factors for coronary artery disease (CAD) [2].

There are some reports that high fasting-insulin level and IR are also associated with in-stent restenosis in nondiabetics [3] and studies have shown that IR is an independent predictor of early restenosis after coronary stenting [4].

However, the impact of IR on major clinical outcomes following percutaneous coronary intervention (PCI) in the drug-eluting stent (DES) era is largely unknown.

Therefore we conducted this study to evaluate the impact of IR on 1-year major clinical outcomes in non-diabetic CAD patients undergoing PCI with DESs.

Methods

Study population

We performed a retrospective observational analysis of 229 consecutive non-diabetic patients with CAD who underwent PCI with DESs from January 2004 to June 2009 at the Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea. We excluded patients

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who were newly diagnosed with diabetes, treated for diabetes, and those who had high fasting glucose (>125 mg/dL) or glycated hemoglobin A1c level (>6.5%).

Patients' baseline demographic characteristics, clinical characteristics, medical history, and procedural data were collected. One-year major clinical outcome data were collected by interviewing at outpatient clinic, telephone interview, and interviewing at the time of routine 6-month follow-up coronary angiography. All patients gave informed consent according to a protocol approved by the Ethics Committee in Korea University Guro Hospital.

Blood sample and biochemical investigation

Blood sampling was done before PCI at fasting state in routine stable PCI. In cases of ST-elevation myocardial infarction (STEMI) undergoing primary PCI or non-STEMI undergoing early invasive strategy, blood sampling was done next day early in the morning following adequate fasting. Samples were collected from venous blood after overnight fasting and blood chemistry was performed. Fasting plasma glucose and insulin were measured and other parameters including the concentrations of serum total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol (LDL-C), creatinine, and high-sensitivity C-reactive protein (hsCRP) were measured. Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), proposed by Matthews et al., whose formula was: HOMA-IR (mg/dL × U/mL) = fasting glucose (mg/dL) × fasting insulin (U/mL)/405 [5]. There were no reports of standard of insulin resistance at HOMA index in Koreans. We used 2.5 as a cut-off point for the analysis; HOMA index ≥ 2.5 was defined as IR group and HOMA index < 2.5 was defined as insulin sensitive group [6].

Percutaneous coronary intervention

Coronary angiography was performed by either femoral or radial approach. Interventional procedure included percutaneous transluminal balloon angioplasty and subsequent DES implantation. PCIs were performed after administration with weight-adjusted bolus of unfractionated heparin (UFH, 70–100 U/kg) or combined administration of low molecular weight heparin (LMWH) and reduced dose of UFH (50 U/kg) during the procedure. During the procedure, patients received UFH to maintain the activated clotting time >250 s. Loading doses of aspirin (200–300 mg) and clopidogrel (300 or 600 mg) were administered before the procedure and followed by aspirin (100 mg/day) and clopidogrel (75 mg/day) after procedure and these dual antiplatelets were maintained at least for 1 year. GP IIbIIIa blocker use was dependent on physician's discretion. Thrombus aspiration was done using Thrombuster II catheter (Kaneka, Osaka, Japan) or Export catheter (Medtronic, Minneapolis, MN, USA) if there were significant angiographic visible thrombi in the target lesion before stenting. After successful wiring to the target lesion, predilation was performed using 2.0–2.5 mm diameter balloons and then stent was deployed. The type of DES was left to the operating physician's choice. Routine angiographic follow up was done at six to nine months after stent implantation.

Study endpoints

Study endpoints were death (cardiac and non-cardiac deaths), non-fatal myocardial infarction, repeat revascularization, and composites of major adverse cardiac events (MACEs) at 1 year. Myocardial infarction included Q-wave myocardial infarction and non-Q-wave myocardial infarction. Revascularization included target lesion revascularization (TLR), target vessel revascularization (TVR), and non-target vessel revascularization (non-TVR). TLR-MACE was defined as the composite of cardiac death, Q-wave myocardial infarction and TLR. TVR-MACE was defined as the composite of total death, any myocardial infarction, and TVR. All MACE (total MACE) was defined as the composite of total death, any myocardial infarction, and any revascularization (TLR, TVR, and non-TVR).

At 6–9 months, routine angiographic follow up was strongly recommended and a variety of angiographic parameters including % restenosis, restenosis lesion length, binary restenosis, restenosis type, late loss, and follow up minimal luminal diameter (MLD) were evaluated between the two groups.

Table 1
Baseline clinical and laboratory characteristics.

Variable, n (%)	IR (n = 54 pts, 23.6%)	Non-IR (n = 175 pts, 76.4%)	p-Value
Male	39 (72.2)	130 (74.3)	0.860
Age, years	63.2 ± 12.4	64.0 ± 11.6	0.616
Current smoking	26 (49.1)	91 (52.6)	0.754
Hypertension	38 (70.4)	99 (56.6)	0.082
Dyslipidemia	9 (16.7)	37 (21.1)	0.563
Prior myocardial infarction	0 (0.0)	2 (1.1)	1.000
Prior CABG	0(0)	1(0.6)	1.000
Prior PCI	4 (7.4)	12 (6.9)	1.000
UA	21 (38.9)	86 (49.1)	0.213
STEMI	3 (5.6)	19 (10.9)	0.302
NSTEMI	9 (16.7)	18 (10.3)	0.229
Total cholesterol (mg/dL)	178.2 ± 47.6	173.4 ± 41.9	0.847
Triglyceride (mg/dL)	137.1 ± 74.9	133.1 ± 86.3	0.941
HDL-cholesterol (mg/dL)	44.0 ± 12.0	44.9 ± 12.9	0.403
LDL cholesterol (mg/dL)	117.6 ± 41.4	112.9 ± 37.1	0.436
Insulin (μm/mL)	18.2 ± 34.8	4.7 ± 2.7	0.002
Glucose (mg/dL)	106.2 ± 12.0	99.5 ± 13.2	0.474
HbA1c (U/mL)	5.8 ± 0.4	5.7 ± 0.6	0.258
HOMA-IR (mg/dL × U/mL)	3.6 ± 1.1	1.1 ± 0.7	0.000
Creatinine (mg/dL)	0.9 ± 0.3	1.0 ± 0.8	0.566
hs CRP (mg/L)	5.4 ± 12.9	13.1 ± 34.8	0.015

Data are mean ± SD or number (%). IR, insulin resistance; CABG, coronary artery bypass graft; Hb, hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; hs CRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 (Statistical package for the social sciences, SPSS-PC Inc., Chicago, IL, USA). Continuous variables were expressed as means ± standard deviation and were compared using Student's t-test. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test. p-Value of 0.05 was considered statistically significant.

Results

A total 229 patients were enrolled, the mean age was 63.8 years, and 73.8% (169/229) were male. Twenty-four percent (54/229) of the patients had IR (HOMA index ≥ 2.5, IR group) and 76% (175/229) patients were insulin sensitive (HOMA index < 2.5, non-IR group).

Between the IR and the non-IR groups, there were no significant differences in cardiovascular risk factors including hypertension, dyslipidemia, and smoking. The concentration of insulin was significantly higher in the IR group compared to the non-IR group. Other laboratory parameters including serum creatinine and individual lipid profiles were not different between the two groups except high sensitivity CRP which was higher in the non-IR group (Table 1). Regarding the lesion locations, the non-IR group had

Table 2
Baseline angiographic and procedural characteristics.

Variable, *n* (%)	IR, *n* (%)	Non-IR, *n* (%)	*p*-Value
Target vessel			0.168
Left main	3(9.1)	6 (4.3)	
RCA	10 (30.3)	33 (23.7)	
LAD	11 (33.3)	75 (54.0)	
LCX	9 (27.3)	25 (18.0)	
Multivessel disease	21 (38.9)	36 (20.6)	0.011
Calcification	13 (24.1)	28 (16.0)	0.222
Lesion length, mm	24.1 ± 12.0	23.5 ± 9.4	0.384
Stent length, mm	24.3 ± 6.0	23.8 ± 6.3	0.850
Stent diameter, mm	3.1 ± 0.4	3.1 ± 0.4	0.564
Post-stenting MLD	2.9 ± 0.5	3.0 ± 0.5	0.988
Type of stent			
SES (Cypher)	16 (29.6)	65 (37.1)	0.334
PES (Taxus)	15 (27.8)	41 (23.4)	0.587
ZES (Endeavor)	12 (22.2)	43 (24.6)	0.856
EES (Xience or Promus)	2 (3.7)	8 (4.6)	1.000

Data are mean ± SD or number (%). IR, insulin resistance; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimal luminal diameter; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent.

lower incidence of multivessel disease as the target vessel (Table 2). Among the different DESs, sirolimus-eluting stent (SES) was more frequently implanted in the non-IR group. However, the stent diameter, length, and post-stenting MLD were not different between the two groups (Table 2).

Angiographic outcomes at 6 months demonstrated that there was a trend toward higher incidence of longer mean restenosis lesion length in the IR group, however other angiographic parameters including follow-up MLD, incidence of binary restenosis, late loss (LL), and mean % in-stent restenosis (>30%) were not different between the two groups (Table 3).

The cumulative MACEs up to 1 year were similar between the two groups despite numerically higher incidence of composite outcomes in the IR group [10 patients (18.5%) in the IR Group and 18 patients (10.3%) in the non-IR Group]. There was 1 patient with cardiac death (1.9%) and 7 patients (13.0%) underwent repeat revascularization in the IR group. There were 3 patients with cardiac deaths (1.7%) and 13 patients (7.4%) underwent repeat revascularization in the non-IR group. There was no difference in the incidence of stent thrombosis up to 1 year between the two groups (Table 4).

The individual clinical endpoints including total deaths, any myocardial infarction, repeat revascularization, TLR-MACE, and TVR-MACE at 1 year were numerically higher in the IR group except non-Q-wave myocardial infarction and coronary artery bypass graft, but those important clinical hard endpoints did not reach statistical difference (Table 4).

Table 3
Six month angiographic outcomes.

Variable, *n* (%)	IR (*n* = 54 pts, 23.6%)	Non-IR (*n* = 175 pts, 76.4%)	*p*-Value
Follow-up MLD (mm)	2.4 ± 0.9	2.5 ± 0.7	0.198
Restenosis lesion length (mm)	25.4 ± 23.9	22.2 ± 16.8	0.087
Binary restenosis (>50%)	5 (9.3)	8 (4.6)	0.193
Late loss (mm)	0.6 ± 0.8	0.6 ± 0.6	0.175
In-stent restenosis (>30%)[a]	8 (14.8)	34 (19.4)	0.548

Data are mean ± SD or number (%). IR, insulin resistance; MLD, minimal luminal diameter.

[a] In-stent restenosis means more than 30% of restenosis.

Table 4
Major clinical outcomes at 1 year.

Variable, *n* (%)	IR (*n* = 54 pts, 23.6%)	Non-IR (*n* = 175 pts, 76.4%)	*p*-Value
Total death	3(5.6)	7(4.0)	0.704
Cardiac death	1(1.9)	3(1.7)	1.000
Non-cardiac death	2(3.7)	3(1.7)	0.337
Any MI	1(1.9)	2(1.1)	0.556
NQMI	0(0.0)	1(0.6)	1.000
QMI	1(1.9)	1(0.6)	0.417
Revascularization	7(13.0)	13(7.4)	0.267
CABG	0(0.0)	1(0.6)	1.000
Repeat PCI	7(13.0)	12(6.9)	0.164
TLR	5(9.3)	8(4.6)	0.193
TVR	5(9.3)	9(5.1)	0.328
Non-TVR	4(7.4)	7(4.0)	0.293
TLR-MACE	6(11.1)	10(5.7)	0.219
TVR-MACE	8(14.8)	15(8.6)	0.198
All-MACE	10(18.5)	18(10.3)	0.151
Stent thrombosis	1(1.9)	1(0.6)	0.417

Data are mean ± SD or number (%). IR, insulin resistance; MI, myocardial infarction; NQMI, non-Q-wave myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization; MACE, major adverse cardiac events.

Discussion

In this study, baseline clinical and procedural characteristics were similar between the two groups, except higher incidence of high sensitivity CRP and the left anterior descending artery as the target vessel.

At 6 months routine angiographic follow up, there was a trend toward longer mean restenosis lesion length in the IR group. However, this worse mid-term angiographic outcome was not translated into worse 1-year clinical outcomes in the IR group.

IR plays a crucial role in the pathogenesis of type 2 diabetes mellitus and also in the development of metabolic disorders accompanied by obesity, dyslipidemia, impaired glucose tolerance, and hypertension. IR is known to be closely associated with various cardiovascular disorders [7–15].

The mechanism how IR predisposes individuals to cardiovascular disease is explained by the development of metabolic syndrome. IR leads to hyperglycemia by abnormal glucose metabolism, and hyperinsulinemia results from elevated levels of blood sugar causing hypertension, low concentration of HDL-cholesterol, and high concentration of serum triglyceride [16–19]. Further, IR has been shown to reduce flow-mediated vasodilation of the brachial artery, cause endothelial dysfunction, trigger inflammatory signaling, increase the formation of advanced glycation end products, and increase mean platelet volume [13,20–23].

Many previous studies have demonstrated that IR is associated with the development of coronary atherosclerosis, plaque instability, and cardiovascular events in patients with or without type 2 diabetes, and hyperinsulinemia was only an indirect indicator for insulin sensitivity and related to cardiovascular disease [14,15,24].

There have been efforts to prove an association between IR and cardiovascular mortality or coronary atherosclerosis on coronary angiography based on hyperinsulinemia as an insulin sensitivity marker [7,14,18,19,25,26]. On the one hand, IR measured by HOMA models is shown to be related with coronary atherosclerosis and restenosis following PCI in non-diabetic patients [3,25–27].

IR as assessed by HOMA index was helpful in the early prognostic stratification, and represented an independent predictor of in-hospital mortality in non-diabetic patients with acute ST-elevation myocardial infarction undergoing primary PCI [28]. Yun

et al. analyzed 98 consecutive non-diabetic patients who underwent elective coronary angioplasty, and revealed that IR (HOMA index $\geq$ 2.6) was an independent predictor of in-hospital and 30-day MACE rates [29].

Therefore we conducted a study to evaluate the impact of IR on 6-month angiographic outcomes and 1-year clinical outcomes in non-diabetic coronary artery disease patients undergoing PCI in the DES era. Our study demonstrated that IR, as assessed by HOMA index, was not relatively uncommon (29%) in a series of all comers based in real-world clinical practice in Korea. Our study showed that the IR group showed worse angiographic outcomes at 6 months, suggesting more extensive and severe atherosclerotic changes in the target lesions even after the DES implantation in non-diabetic patients underwent PCI with DESs in real world clinical practice as compared with those of the non-IR group. However, these angiographic results were not translated into differences in major clinical outcomes at 1 year, probably due to less chance of recurrence following DES implantation, inherent limitation by baseline differences in retrospective analysis, relatively small study population, and shorter period of clinical follow up. Our study results are hypothesis-generating in the DES era and further randomized clinical study with larger study population with long-term clinical follow up will be needed to make the final conclusion. Further, assessment of clinical outcomes by subanalysis according to different subgroups comprising different risk factors and acute coronary syndromes would be needed with a larger study population to get more detailed information.

Study limitations

Although the major clinical outcomes were not different between the two groups, with a larger study population, more prolonged follow up may lead to different results. Because of the following contributing factors, this result can be a hypothesis-generating message and we need more data to make a final conclusion. First, there were different baseline angiographic and procedural characteristics due to the limitation of retrospective analysis, specifically a trend toward higher chance of multivessel disease in the IR group. Second, we did not evaluate important baseline characteristics associated with IR such as body mass index and waist circumference. Third, 6-month angiographic outcomes in the IR group tended to be worse and these findings may lead to clinical differences with a larger study population and extended clinical follow up. Fourth, all the study population underwent PCI with DESs and this will limit the recurrence of target lesions and may contribute to minimizing the development of differences in major clinical outcomes in both groups.

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